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RELATIONSIP OF SMOKING AND ALCOHLISM TO MULTI DRUG RESISTANT TUBERCULOSIS: A HOSPITAL BASED STUDY

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ABSTRACT
Alcohol consumption and smoking are an important risk factor for tuberculosis. A meta-analysis conducted by LÖNNROTH *et al*[1], which included studies published up to 2007, indicated that diagnosis of an alcohol use disorder resulted in a nearly three-fold increase in the risk of tuberculosis. Based on this meta-analysis, alcohol consumption was estimated to be responsible for approximately 10% of all incident cases and deaths due to tuberculosis. This study was also conducted to assess the correlation of smoking and alcoholism as risk factors for tuberculosis.

KEYWORDS: Alcohol consumption, tuberculosis.

INTRODUCTION
Tuberculosis (TB) is a chronic infectious disease caused by the bacterium Mycobacterium tuberculosis (MTB) and remains one of the leading causes of death worldwide, despite the availability of effective anti-TB drugs.[2] Globally, there were an estimated 10.4 million new TB cases and 2.0 million deaths due to the disease in 2016.2 The number of new cases increased from 9 million in 2013 to 10.4 million in 2016.[3,4]

Several risk factors have been considered for DR-TB.[5-8] Previous treatment ranks as the strongest and most frequent determinant of DR-TB,[5,7] and diabetes mellitus is also considered as an independent risk factor, especially for primary MDR-TB.9 Other factors include HIV infection, younger age, and being foreign born.[5,8-10]

Since both tobacco smoking and MDR-TB are global problems, the association between tobacco smoking and MDR-TB has attracted much attention from researchers. However, previous studies on the association between tobacco smoking and MDR-TB were varied in regard to geographic region, ethnicity, and study design. Moreover, epidemiological data on this association have not been systematically reviewed. Therefore, we conducted a study to determine whether tobacco smoking was an independent risk factor for MDR-TB, and our results may help to guide health interventions.

MATERIAL AND METHOD
The study was conducted in the department of Respiratory Medicine, MMIMSR between for period of two years, 100 patients of PTB who were admitted in the Respiratory Medicine ward or reported in OPD and who had fulfilled the criteria that is they were sputum positive pulmonary TB or sputum negative retreatment cases were considered for the study. The patients who fulfilled inclusion criteria and after verifying the exclusion criteria were finally taken up for the study.

Inclusion Criteria (Based on PMDT Guidelines)
Criteria A
1. All failures of new TB cases
2. Smear +ve previously treated cases who remain smear +ve at 4th month onwards
3. All pulmonary TB cases who are contacts of known MDR TB case

Criteria B – in addition to Criteria A
1. All smear +ve previously treated pulmonary TB cases at diagnosis
2. Any smear +ve follow up result in new or previously treated cases

Criteria C – in addition to Criteria B
1. All smear -ve previously treated pulmonary TB cases at diagnosis.

Exclusion criteria

1. Presence of immunodeficiency conditions such as
a. HIV / AIDS.
b. Organ transplantation.
c. Malignancy
2. Extra-pulmonary TB and/or patients requiring surgical intervention.
3. Patients unwilling to take part in study.

Study Sequence

Hundred patients who were smear positive or sputum negative retreatment cases were selected for the study. A written consent was obtained from each of these patients or their close relatives. These 100 patients were asked to submit their two sputum samples at least one morning and one spot sample. Up to 5 ml of sputum samples were collected in 50 ml falcon tubes marked A and B. The tubes were sealed with parafilm and labeled mentioning name of patient, sample A and sample B and date of collection on the specified rectangular space provided on the side of falcon tube using permanent marker pen. Annexure I was filled up mentioning the detail of patients. The duly labeled samples were individually packed in zip lock poly bags and placed in thermocol boxes after ice-gel packs below and above falcon tube packs following international guidelines for transportation of infectious substances. Annexure I was kept in separate poly bag inside the box. Then these samples are handed over to designated courier agency hired by District TB Officer, Ambala immediately so as to reach IRL Haryana Govt. Public Health Laboratory, Karnal within 72 hours of collection. These samples are received in the designated laboratory. Date of receipt was mentioned on the box and soon afterwards the samples are processed for evaluation of drug susceptibility pattern by MTB RIF/INH Line Probe Assay method. The tuberculosis patients admitted as inpatients or visited O.P.D. were subjected to thorough history taking, regarding clinical features and previous treatment. Patients who satisfied the inclusion criteria were included in the study with their consent. They were examined in detail and the study Performa was filled .Similar exercise was carried out with the outpatients, who were examined on their firstvisit and were regularly followed up. All the patients underwent HIV testing, chest x-ray imaging and sputum microscopy.

Classification of Sputum

Zn staining grading(RNTCP)	Reporting/ grading
>10 AFB per field after examination of 20 fields	Positive 3+
1-10 AFB per field after examination of 50 fields	Positive 2+
10-99 AFB per 100 fields	Positive 1+
1-9 AFB / 100 fields	Positive scanty
No AFB per 100 fields	negative

Sputum Samples Collection guidelines

Collection container: 50 ml sterile falcon tube
Storage Requirements: Room temperature 15-20 degrees Celcius refrigeration temperature.
Transport Conditions: Thermocol boxes with cold chain system maintaining temperature 15-20 degrees Celcius. If delay in transport of more than 1 hour expected, then samples were to be refrigerated.

If the Sample quantity was less than 2 ml, Samples containing frank blood and New Pulmonary TB cases were rejected.

Patients were instructed to rinse the mouth and gargle with warm or fresh water prior to sputum collection. Also, two sputum samples were to be collected in falcon tubes provided, both morning samples or at least one morning sample and one spot sample. No food particles should have been there in the samples and approximately 5 ml of sample was needed for processing. Fresh mucoid material (free of salivary secretions) produced by deep coughing was collected with the patient being supervised as needed and deliver promptly to the laboratory.

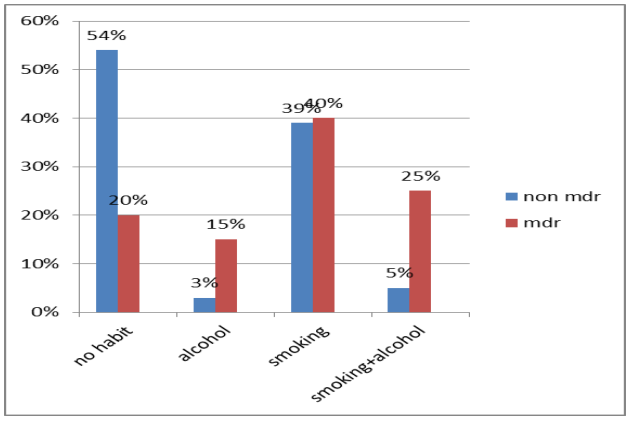
RESULTS

This study done was done in MMIMSR Hospital for a period of two years. It incorporated a sum of 100 (n-100) category II pulmonary TB patients, sputum positive as well as negative. Patient populace was partitioned into two gatherings of MDR (n-20) and Non MDR (n-80) as indicated by the drug susceptibility results. After that the prevalence of MDR was determined which was **20 %(n=20).**These two gatherings were then examined to search for measurable association and statistically significant association between smoking, alcoholism and MDR TB .

Table No. 1: Habits in groups: (chi square test).

Habits		MDR		Non MDR		X^2	P- Value
		n	%	n	%		
No Habit	Present	4	20%	43	54%		
	Absent	16	80%	37	46%		
Alcohol	Present	3	15%	2	3%		
	Absent	17	85%	78	97%	5.2632	.021781
Smoking	Present	8	40%	31	38%		
	Absent	12	60%	49	62%	0.0105	.918351
Smoking+Alcohol	Absent	5	25%	4	5%		
	Present	15	75%	76	95%	7.8144	.005183

In habits statistically significant association was seen between alcohol abuse and groups and smoking plus alcohol and groups, however smoking and groups did not show statistically significant association. P value for alcohol abuse = 0.021 and p value for smoking plus alcohol = 0.0051. In MDR group 40% smoked (n=8) compared to 38 %(n=31) in Non MDR group. In MDR group 15 %(n=3) had alcohol as compared to 3 %(n=2) in Non MDR group. In MDR group 25 %(n=5) both smoked and had alcohol as compared to Non MDR group where 5 %(n=4) smoked and had alcohol. In smoking + alcohol group, people who only smoked or only abused alcohol were not taken but this group was taken as separate entity.



Habits in MDR and Non MDR group

DISCUSSION

Smoking is a known risk factor for tuberculosis with studies showing two fold increase of risk of progression to active tuberculosis[11], similarly alcohol consumption according to studies too increases the risk of development of tuberculosis up to three times with consumption of around 40 g or more alcohol per day.[12] In our study in MDR group 15 %(n=3) had alcohol alone, 40%(n=8) were smokers and 25% were both alcoholic and smoker in MDR group and there is a statistically significant association between alcoholism and MDR TB. P value =0.02 and people who both smoked and had alcohol p value = 0.005, statically significant association between smoking alone and MDR TB was not seen. Very few studies have been done on subject of MDR TB and alcoholism and MDR TB and smoking our study is a hospital based study with small sample size. So more national level studies are required on this subject. A few studies I would like to point out which show statically significant association between alcoholism and MDR TB are, a study by Garcia etal[13] in Madrid Spain titled "risk factors of Multi Drug Resistant Tuberculosis in a tuberculosis unit in Madrid Spain" showed statistically significant association between alcohol abuse and MDR TB. Similarly a study by Skraihnaet al[14], titled "Multi Drug Resistant Tuberculosis in Belarus: The size of problem and associated risk factors" showed statically significant association between alcohol abuse, and MDR TB, as well as smoking and MDR TB.

It is estimated that, worldwide, 1.3 billion people consume tobacco and that most of them live in underdeveloped or developing countries, where the tuberculosis rates are also higher.[15] Therefore, the greatest impact of smoking in terms of public health issues related to infection is probably the increase in the risk of tuberculosis. Some systematic reviews and meta-analyses of observational studies have shown an unfavorable association between the global epidemics of tuberculosis and smoking, exposure to tobacco smoke having been associated with tuberculosis infection, active tuberculosis, and tuberculosis-related mortality.[16,17]

The role that cigarette smoke plays in the pathogenesis of tuberculosis is related to ciliary dysfunction, to a reduced immune response, and to defects in the immune response of macrophages, with or without a decrease in the CD4 count, increasing susceptibility to infection with *Mycobacterium tuberculosis*.[15] The alveolar macrophage binds to the bacillus through complement receptors 1, 3, and 4. Activated lymphocytes release cytokines while recruiting macrophages, fibroblasts, and other lymphocytes. The major cytokine involved in granuloma formation is TNF-α, which is released by macrophages immediately after exposure to *M. tuberculosis* antigens. The TNF-α activates macrophages and dendritic cells. In smokers, nicotine, acting through the α7 nicotinic receptor, reduces the production of TNF-α by macrophages, thereby preventing its protective action and favoring the development of tuberculosis.[18,19]

Secretion of IL-12 by macrophages induces the production of IFN-γ in natural killer cells. This immune response aspect, known as the Th1 response, aims to destroy *M. tuberculosis* by forming a fibrous granuloma. Cigarette smoke selectively promotes low production of interleukin-12 and TNF-α, impeding granuloma formation, which would contain the infection at this stage in immunocompetent individuals, smoking therefore creating conditions that allow the development of active tuberculosis.[18,19]

Tuberculosis-related mortality rates are significantly higher in smokers than in never-smokers.[20]Among individuals without a history of tuberculosis, the risk of death due to tuberculosis is nine times higher for smokers than for never-smokers.[20] One recent study showed that smoking and HIV infection were significant risk factors for mortality in patients with MDR-TB.[21] When smokers quit smoking, the risk of death due to tuberculosis drops significantly (by 65% compared with that observed for those who continue smoking), which indicates that smoking cessation is an important factor in reducing tuberculosis-related mortality.

A prospective study, conducted in rural China in 2017, underscored the supposition that smoking is an independent risk factor for tuberculosis infection, especially in elderly smokers, as well as demonstrating a direct correlation between smoking history (packyears)

and the risk of latent tuberculosis.[22] Recent investigations suggest that, in the detection of latent tuberculosis with IFN-γ methods, the proportion of false-negative results is higher among smokers than among nonsmokers, and that smoking has a negative impact on the results of tuberculosis treatment, delaying conversion of the sputum culture during the treatment and extending the time of treatment.[23] Likewise, nicotine withdrawal has been shown to be strongly associated with successful completion of the treatment for latent tuberculosis.[24] A study conducted in Brazil showed that men with a history of tuberculosis are 4.1 times more likely to present airway obstruction than are those with no such history, and those results remained unchanged after having been adjusted for age, gender, level of education, ethnicity, smoking, exposure to dust or smoke, respiratory morbidity in childhood, and current morbidity. In conclusion, a history of tuberculosis is associated with airway obstruction in middle-aged and older adults.[25] Passive and active exposure to cigarette smoke are both associated with an increased risk of infection with M. tuberculosis and of the development of active tuberculosis. A qualitative systematic review, published in 2007, highlighted the strong correlation between smoking and active tuberculosis, as well as showing that passive smoking correlated moderately with active tuberculosis and with the need for retreatment.[26] A history of parental smoking is already part of the investigation of episodes of respiratory infection in children. A recent study also showed that the risk of infection with M. tuberculosis was increased in children living in a region endemic for tuberculosis, and that parental smoking was significantly associated with the risk of active tuberculosis, even after having been adjusted for associated factors.[27] Therefore, the effects of passive smoking are also a concern regarding active tuberculosis, and every smoker with tuberculosis should be educated about the harm that their addiction can cause to other individuals, especially their contacts, who are at greater risk of contracting active tuberculosis. A study of children who were household contacts of tuberculosis patients showed that exposure to passive smoking, as confirmed by the measurement of urinary nicotine levels, is a major risk factor for active tuberculosis (OR = 5.39; 95% CI: 2.44-11.91).[28]

Another crucial point in the control of tuberculosis is the abandonment of treatment. Smoking has been associated with the abandonment of tuberculosis treatment, and that association has been found to be independent of alcohol or illicit drug use.[29] Therefore, abandonment of tuberculosis treatment might be related to the psychosocial aspects of smoking, the predominance of males, and the lower socioeconomic status of the affected populations, all of which are factors associated with lower rates of adherence to treatment.[29] The recognition of that association is of paramount importance in combating exposure to tobacco smoke in order to reduce the risk of tuberculosis, as is simultaneous treatment for smoking and tuberculosis, both of which mainly affect the respiratory system. Because the smoking epidemic is increasing in some parts of the world and tuberculosis control is still far from being achieved, the prospects are quite worrisome. In one study, a mathematical model was applied in order to evaluate the impact of smoking on the incidence of tuberculosis, that impact being calculated on the basis of the trend in smoking, as well as on the projections for tuberculosis incidence, prevalence, and mortality from 2010 to 2050.[30] The authors estimated that smoking will produce in excess of 18 million tuberculosis cases and 40 million deaths if the number of smokers around the world continues to increase at the current rate. They also estimated that, between 2010 and 2050, smoking will be responsible for a 7% increase in the number of new cases of tuberculosis (from 256 million to 274 million) and a 66% increase in the number of tuberculosis-related deaths (from 61 million to 101 million), making it even more problematic to reach the tuberculosis control targets set by the WHO.[30] For a tuberculosis control program to be effective in daily clinical practice, patients with tuberculosis should be encouraged to undergo smoking cessation treatment, which can also improve the quality of life of such patients.

Although the consumption of alcohol is considered socially acceptable worldwide, it can lead to dependence. Alcohol consumption problems vary widely. The harmful use of alcohol ranks among the top five risk factors for disease, disability, and death, as well as being a causal factor in more than 200 disease and injury conditions, including tuberculosis, worldwide.[31] It has been estimated that approximately 10% of all tuberculosis cases are attributable to alcohol use.[32] One major obstacle to making a diagnosis of alcohol abuse is the difficulty in quantifying alcohol intake. According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, published by the American Psychiatric Association, alcohol use disorder (AUD) is a chronic, relapsing brain disease characterized by an impaired ability to stop or control alcohol use despite adverse social, occupational, or health consequences. The presentation of AUD can range from mild to severe, and recovery is possible regardless of the level of severity.[33] The prevalence of AUD among tuberculosis patients varies depending on the population studied. Russia and countries of the former Soviet Union are among the regions most critically impacted by alcohol use. In a cohort of individuals starting tuberculosis treatment in Tomsk, Siberia, 60.2% had a lifetime history of AUD and, most importantly, approximately 28% were female.[34] In a prospective study conducted in New York City, a cohort of individuals with AUD were followed for 8 years and the incidence of tuberculosis was found to be 464 cases/100,000 person-years, which was 9 times the incidence found for the age-matched general population.[35]

The association between alcohol use and tuberculosis has long been known, although there have been inconclusive

findings related to various confounding factors, because it is still not known whether the increased risk of tuberculosis is due to the use of alcohol per se or because of the sequelae of AUD, such as liver damage and nutritional deficiency, or social factors, such as crowding, malnutrition, homelessness, and imprisonment, independently of the alcohol consumption. However, in vivo and in vitro studies have demonstrated that alcohol use significantly disrupts the immune response, increasing susceptibility to respiratory diseases such as tuberculosis.[36]

Various population-based studies have shown that there is a strong association between AUD and tuberculosis.[37,38] In a meta-analysis that included 3 cohort studies and 18 case-control studies,[39] heavy alcohol use (defined as ≥ 40 g alcohol per day) or a clinical diagnosis of AUD was found to have a pooled relative risk for the development of active tuberculosis of 3.50 (95% CI: 2.01-5.93). Neither exclusion of the smaller studies (because of suspected publication bias) nor adjustment for various sets of confounders altered the results significantly. In a prospective study conducted in China, a cohort of adults were followed for a mean of 16.8 ± 5.2 years. [40] The authors found that alcohol consumption (≥ 2 drinks per day) were associated with an increased risk of tuberculosis when accompanied by smoking (hazard ratio = 1.51; 95% CI: 1.11-2.05), which is another risk factor for the development of active tuberculosis.[41]

Alcohol abuse influences not only the incidence of tuberculosis but also its clinical evolution and outcome. Individuals with AUD are considered more infectious because AUD has been associated with the finding of cavitary disease on chest X-rays and therefore with smear positivity.[41,42] In addition, AUD has been associated with higher rates of treatment default (OR = 1.99; 95% CI: 1.04-3.81) and relapse (OR = 3.9; 95% CI: 2.5-6.1)[43,44] There are several reasons for that, including precarious living conditions and the increased risk of hepatotoxicity due to tuberculosis treatment in this group of patients.[45]

Whether alcohol abuse increases the risk of MDR-TB is not well established. In a case-control study conducted in Botswana, the prevalence of alcohol use was found to be higher among the individuals with MDR-TB than among those in three different control groups, even after adjustment for several confounders.[46]

Ensuring healthy lives and promoting well-being for individuals of all ages are among the United Nations Sustainable Development Goals for 2030, calling for the prevention and treatment of substance abuse, including the harmful use of alcohol. [47] It is clear that AUD has a negative impact on tuberculosis risk and treatment outcomes. Therefore, in populations at high risk for AUD, it is important to evaluate this condition, integrating the management of AUD and the treatment for tuberculosis, as well as to monitor treatment adherence in order to avoid default and to follow patients closely to identify adverse events.

Prevalence of MDR TB was found to be **20%** which was comparable to studies done by Sharma et al [48] at Delhi and another study done by Jain et al [49] at Lucknow which showed prevalence around 20.4 % and 19.8% in retreatment cases respectively shows MDR TB prevalence in different parts of country, in studies undertaken at different point of time.

Prevalence of MDR TB in different parts of India.

Location	Period of Study	Prevalence of MDR TB %
Gujarat	1983-1986	30.2%
Delhi	1990-1991	33%
Haryana	1991-1995	49%
Delhi	1996 -1998	14%
Bangaluru	1999-2000	12.8%
Tamil Nadu	1999-2003	11.8%
Ahmadabad	2000-2001	37%
Gujarat	2002-2007	17.2%
Delhi	2006	47.1%

According to WHO report 2013 the incidence of MDR TB in new cases is 2.2% and in retreatment cases its 15 % but there are some other studies like one done by Paramsivan et al [68]which was retrospective study of 2816 these patients were repeatedly treated and prevalence found was 53 % so we can deduce safely from data above from all parts of India that MDR prevalence varies from place to place and study to study, hence a large nationwide study is the need of the hour.

In our study samples were sent to IRL KARNAL they used L.P.A. molecular assay so in our study resistance or sensitivity to only Isoniazid and Rifampicin was noted, and not other three first line drugs, by W.H.O. definition resistance to at least Isoniazid and Rifampicin with or without resistance to other drugs constitutes MDR TB. In our study 20 %(n=20) were MDR cases that is resistant to both drugs and there were two cases of mono resistance to Isoniazid alone(2%) and no case of mono resistance to Rifampicin were observed in our study.

Now if compared to study done by Sharma et al [48] they used mycobacterial culture and drug susceptibility testing(DST) Isoniazid mono resistance was not noted, Rifampicin mono resistance was noted in 1.5 %(n=3) cases ,resistance to H+R+S was noted in 2.04%(n=4) cases and H+R resistance was noted in 18.4% cases (n=36). So in total 20.44 %(n=40) cases were MDR cases which is very comparable to data we obtained by L.P.A. ,similarly Dholakia N et al[69] encountered 11 % cases of mono resistance and 14 % were MDR. Jain et al[49] found MDR prevalence to be 19.8%. Comparison of our study with study done by Sharma et al.

Drugs	Present study % n=100	Sharma et al[48] % n=196
Isoniazid	2%(n=2)	0%(n=0)
Rifampicin	0%(n=0)	1.5%(n=3)
Streptomycin	n.a.	0%(n=0)
R+H+S	n.a.	2.04%(n=4)
H+R	20%(n=20)	18.4%(n=36)
MDR	20%(N=20)	20.44%(N=40)

CONCLUSION

As concluded by our study there is an association between tuberculosis and smoking as well as alcoholism. Nationwide studies are yet to reach conclusion with regard to MDR TB`s association with smoking, alcoholism and this being a hospital based study larger studies are need of hour. Similarly association was found between fever and MDR TB, hemoptysis and MDR TB, and breathlessness and MDR TB but once again sample size being only 100 and this being a hospital based study more nationwide studies are need of the hour.

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